
Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**October 2014
Drug Safety**

Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen Guidance for Industry

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Contains Nonbinding Recommendations

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Guidance for Industry¹

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help drug manufacturers, packagers, and labelers minimize the risk to consumers of acetaminophen-related liver damage associated with the use of nonprescription, also known as over-the-counter (OTC), acetaminophen-containing pediatric liquid drug products. Generally, these products are marketed under the OTC Drug Review (FDA's Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (the IAAA TFM)).² FDA plans to address portions of the tentative final monograph through the notice and comment rulemaking process. In the meantime, however, to encourage safer use of these products, we are providing recommendations for acetaminophen concentration, container labels and carton labeling, and packaging of such products and providing recommendations regarding any associated delivery devices. FDA's recommendations are designed to encourage safer use of these products by minimizing the potential for acetaminophen overdosing due to medication errors or accidental ingestion. Unless specified, these recommendations apply to both single ingredient and combination ingredient OTC liquid oral drug products (such as suspensions, solutions, elixirs, and syrups) that are labeled for use by children under 12 years of age and contain acetaminophen.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at FDA.

² "Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph," 53 FR 46204, (November 16, 1988). Available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Over-the-CounterOTCDrugs/StatusofOTCRulemakings/UCM078460.pdf.

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II. BACKGROUND

Acetaminophen is marketed in many OTC drug products as a pain reliever and fever reducer. A majority of OTC acetaminophen products are currently marketed under the conditions stated in the IAAA TFM. In addition to the drug labeling requirements described in section 502 of the Federal Food, Drug, and Cosmetic Act (FD&C or the Act) (21 U.S.C. 352) and in Title 21 of the Code of Federal Regulations, Part 201, OTC acetaminophen products must also be labeled with liver injury warnings and other required information pursuant to 21 CFR 201.326. The agency allows acetaminophen to be marketed without approval of a new drug application³ in accordance with the IAAA TFM and when the required acetaminophen-related warnings and other labeling requirements in § 201.326 are met. However, OTC pediatric liquid oral drug products containing acetaminophen have been associated with overdoses due to medication errors that resulted in serious adverse events including severe liver damage and death. In particular, there have been many reports of overdose attributed to confusion between concentrated acetaminophen drops (80 mg/0.8 mL and 80 mg/mL) and acetaminophen oral liquid (160 mg/5 mL).

This guidance is part of FDA's ongoing initiative to reduce the risk of acetaminophen-related liver injury associated with all OTC and prescription acetaminophen-containing products. As part of that initiative, in June of 2009, three FDA committees, the Drug Safety and Risk Management Advisory Committee, the Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, met jointly to consider a range of risk reduction measures. Among other measures, the Advisory Committees recommended moving to a single, standardized acetaminophen concentration for OTC pediatric liquid drug products, because the availability of multiple concentrations causes confusion and errors among both consumers and healthcare professionals.⁴

In May of 2011, FDA convened a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee to discuss the use of acetaminophen in children.⁵ Shortly before the meeting, the Consumer Healthcare Products Association (CHPA) voluntarily proposed to phase out all of the existing concentrated drop formulations of the OTC, single-ingredient, oral, liquid acetaminophen drug products for pediatric use and market only the 160 mg/5 mL formulation.⁶ At the Advisory Committee meeting, FDA took note of CHPA's voluntary transition to a single concentration of pediatric liquid acetaminophen. Among other

³ See generally section 505 of the FD&C Act and 21 CFR Part 314.

⁴ Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee, held June 29-30, 2009, are available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM179888.pdf>.

⁵ Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, held May 17-18, 2011, are available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/UCM264147.pdf>.

⁶ See May 4, 2011, CHPA press release entitled "OTC Industry Announces Voluntary Transition to One Concentration of Single-Ingredient Pediatric Liquid Acetaminophen Medicines," available at http://www.chpa.org/05_04_11_PedAcet.aspx.

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recommendations, the Advisory Committees recommended the use of a flow restrictor or another feature designed to prevent excessive dosing, use of a safety dosing syringe to reduce accidental ingestion by children, and marking dosage delivery devices in milliliters only.⁷

In response to CHPA's voluntary transition to a single concentration of OTC liquid acetaminophen products, FDA published a Drug Safety Communication on December 22, 2011, to inform the public of the 160 mg/5 mL concentration now marketed for children ages 2 to 3 years and to recommend that end users of the product read the Drug Facts label to identify the concentration of the liquid acetaminophen, dosage, and directions for use.⁸

FDA is issuing this guidance to address ongoing concerns about the potential for acetaminophen overdose associated with these products and to promote their safe use. Besides overdose due to confusion associated with the multiple pediatric formulations with varying concentrations, there have also been reports of overdose attributed to:

1. Concomitant administration of two products containing acetaminophen;⁹
2. Inadequate prominence of the depiction of concentration on container labels and carton labeling;
3. Dosage delivery device not being packaged with the medication;
4. Poorly designed delivery devices (e.g., devices with difficult-to-read markings or device designs that make it difficult to dispense a precise dose); and
5. Inconsistent and/or confusing units of measurement (e.g., cc, mL, tsp, and tbsp) under "Directions" in the Drug Facts Panel and elsewhere in labeling.

We note that FDA issued a Guidance for Industry on dosage delivery devices in 2011 to help address bullet numbers 3 to 5.¹⁰

In addition to overdoses due to dosing errors, there have been reports of overdose from accidental ingestion by children.

III. RECOMMENDATIONS

To avoid confusion and the potential for dosing errors, FDA recommends that OTC oral liquids containing acetaminophen for pediatric use be formulated, packaged, and labeled as described below. Unless noted otherwise, the following recommendations apply to both single ingredient

⁷ See May 2011 Minutes, pp. 6-7.

⁸ FDA Drug Safety Communication: *Addition of another concentration of liquid acetaminophen marketed for infants*, available at <http://www.fda.gov/Drugs/DrugSafety/ucm284741.htm>.

⁹ Mitigating the risk of concomitant administration is addressed in the *Organ-Specific Warnings: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use — Small Entity Compliance Guide*, July 2010. See Table 2 of the guidance, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM222733.pdf>.

¹⁰ FDA guidance for industry *Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products*, May 2011, available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM188992.pdf>.

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and combination OTC liquid oral drug products that contain acetaminophen and are labeled for use by children under 12 years of age.

Product Concentration

- All single-ingredient acetaminophen oral liquids for pediatric use marketed under the conditions specified in the IAAA TFM should have a concentration of 160 mg acetaminophen per 5 mL.

Label and Labeling

- For single-ingredient acetaminophen oral liquids, the statements “160 mg/5 mL” or “160 mg per 5 mL” should be prominently presented on the principal display panel (PDP) of the container label and carton labeling immediately below or to the right of the active ingredient name (i.e., acetaminophen) and in the same font size as the active ingredient name.
- The PDP should clearly indicate the age range and units of age (e.g., months or years) as stated in the Drug Facts Panel under the heading “Directions.”
- If a manufacturer uses a Quick Response (QR) Code,¹¹ we recommend that it appear on the side or back panel of the container label or carton labeling, away from the bar code and in a size that does not compete with or distract from the presentation of other required or recommended information on the label or labeling.
- If there is an image of a child on the PDP, the image should be representative of the age group identified under “Directions” in the Drug Facts label. For example, a product labeled for use by children two years of age or older should not show an infant on the PDP.
- Use of the word “new” should always include a statement that specifies what is new about the product (such as new directions or a new delivery device). This statement should be in conjunction with and with the same prominence as the word “new.” Unless required by the Agency, any statement describing the product as “new...” should not appear for a period longer than 6 months.
- The dosing directions in the Drugs Facts label should be provided only in milliliters (mL).
- An image or picture of the dosage delivery device packaged with the product should appear on the PDP. It should be located on the lower half of the PDP and the dosage

¹¹ A Quick Response (QR) Code is a matrix bar code (or two-dimensional bar code) that can be read by a mobile phone. QR codes may provide a range of information (e.g., Internet address and phone numbers). FDA has not developed a formal position on the use of QR Codes.

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delivery device should appear empty to avoid suggesting that the image or picture is illustrating the dose or volume to be administered.

Drug Delivery

- The product package should include an appropriate dosage delivery device, such as a calibrated and labeled oral syringe or dosing cup.¹⁰
- As the dosing directions should be in milliliters (mL), accordingly the dosage delivery devices should have calibrated units of liquid measurement expressed in milliliters (mL) only.
- The use of droppers, such as a dropper that is made up of a glass or plastic stem and rubber bulb, is discouraged, because it is difficult to measure an accurate dose using a dropper.
- If a firm wants to provide a dosage delivery device other than a standard measuring device, it should conduct usability studies before the device is introduced into the market to ensure the device can be easily understood and accurately used by consumers.¹² In such cases, we encourage the firm to discuss the proposed innovative dosage delivery device with FDA before introducing the device into the market.
- We recommend the adoption of container features designed to improve safety by potentially contributing to more accurate dosing and helping to reduce the incidence and magnitude of accidental acetaminophen ingestion by children, such as an appropriate flow restrictor contained in the opening of the immediate container. If a flow restrictor is included, it should be attached to the container in a way that prevents it from being pushed into the bottle or easily removed. Firms are encouraged to discuss innovative containers/packaging features with FDA before introduction into the market.¹³

¹² Although this guidance is not intended to address the adequacy of dosage delivery devices to deliver the labeled dosage, the Agency may consider issuing future guidance to industry that addresses topics such as age, weight, solubility, viscosity, patient populations, and instructions for cleaning, reuse, and storage.

¹³ We note that if applicable these products must be compliant with the poison prevention packaging standards found in Title 16 of the Code of Federal Regulations §1700.15 (16 CFR 1700.15).